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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MITCHELL, LAURA MCGILLEM

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,913	ARENAS ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/29/2007 has been entered.

Claims 1-3 and 5-12 are under examination. Claims 4 and 13-69 are cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowen et al (of record) in view of Takeshima et al (of record).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 7/29/2005 and for reasons outlined below.

Applicants have submitted REMARKS on 5/29/2007, as well as a Declaration by Dr P. Sacchetti on 6/19/2007 accompanied by comments by Attorney Hagan. These will be addressed below. It appears that the majority of the comments by Attorney Hagan

are a summary of the Sacchetti Declaration and will be addressed with the Sacchetti Declaration.

In REMARKS:

Applicants submit that the thrust of Applicant's argument in the previous Pre-Appeal Brief Request for Review was the Examiner's failure to satisfy the criteria for establishing *prima facie* obviousness, according to §706.02(j) of the Manual of Patent Examining Procedure. These criteria were based on decisions of the Court of Appeals for the Federal Circuit, including *In re Vaeck*, 20 USPQ2nd 1438 (Fed. Cir. 1991), involving application of the so-called teaching, suggestion, motivation (or TSM) test for non-obviousness.

Applicants briefly discuss the review of the appropriate framework for determining non-obviousness under 37 USC § 103(a) by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.*, S.Ct. 2007 WL1237837 (U.S.). Applicants submit that the U.S. Patent and Trademark Office released a memorandum instructing examiner's that, in formulating a rejection under 35 USC §103(a), based upon a combination of prior art elements, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed". See May 3, 2007 memo of M.A. Focarino, Deputy Commissioner for Patent Operations. Applicants submit that in the present case, the Examiner has failed to identify any plausible reason why a person of ordinary skill in the art would have combined elements of Bowen et al and Takeshima et al in the matter claimed by applicants herein.

Applicants submit that neither Bowen et al and Takeshima et al describes culturing a neural stem cell or neural progenitor cell with an astrocyte of the ventral mesencephalon. Applicants submit that neither reference individually or in combination can, therefore, possibly render obviousness the claimed invention, involving treatment of a neural stem cell or neural progenitor cell as claimed.

Applicants submit that Bowen describes only a method for generating dopaminergic cells by the induction and endogenous expression in CNS stem cells of a gene coding for the nuclear receptor Nurrl in order to direct such neuronal precursors to a dopaminergic cell fate, which is verified by expression of tyrosine hydroxylase (TH). See the abstract and examples 1 and 2 of Bowen. In the background section, Bowen discloses that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media from striatal astrocytes has been shown to increase the survival of the neurons. See column 3, lines 11-25 of Bowen.

Applicants submit that Takeshima is cited as purportedly providing the reason why a person skilled in the art would have arrived at the combination of the reference disclosures in the manner proposed by the Examiner. Applicants submit that the Examiner's reliance on Takeshima for this purpose is plainly misplaced. Applicants submit that there is no mention of neuronal stem cells or neural progenitor cells in Takeshima. Indeed, the term "development of TH^+ neurons", as used in Takeshima, when properly considered in context, does not include neural stem cells or neural progenitor cells. Applicants submit that the "development of TH^+ neurons" is properly interpreted as the maturation of the neurons, and not inducement of neuronal fate, as

presently claimed. Takeshima refers, at page 816, under the heading "Discussion", to "three distinct phases of development" and at page 817 to "the distinct phases of development identified in this study". These phases of development are (i) a progressive neurite development phase; (ii) an adverse growth phase; and (iii) a surge of neuritic growth phase as illustrated, in part, in Figure 5 of Takeshima et al. These are phases of development of cells already committed to a neuronal fate. Applicants submit that considering the limited context of "development" discussed in this reference, there is no factual basis provided in Takeshima for extrapolating the term "development of TH^+ neurons", so as to include neural stem cells or neural progenitor cells.

Applicants submit that the Examiner has utilized impermissible hindsight in assessing non-obviousness. Applicants submit that Takeshima neither treated the cells that are actually subject to the present invention, i.e. neural stem and progenitor cells, nor observed the result claimed, i.e. induction of a dopaminergic neuronal fate. Applicants cite Takeshima's results, purpose, ultimate goal and conclusion that an astrocyte-derived NTF that is relatively specific for promoting the survival of the dopaminergic neuronal phenotype is believed to mediate the observed effect.

Applicants submit that one of ordinary skill in the art would search Bowen and Takeshima in vain for any reason, much less a technically plausible reason, for attempting to treat different cells to achieve a different result. Indeed, Applicants submit that neither Bowen nor Takeshima contains the slightest suggestion to use what is disclosed in one reference in combination with what is disclosed in the other reference. Cf. *In re Avery*, 186 USPQ 161 (CCPA 1975). That being the case Applicants submit

that it cannot reasonably be maintained that the combined disclosures of Bowen and Takeshima fairly suggest doing what the applicants have done.

Applicants have filed a Declaration under 37 CFR 1.132 by Dr. Paola Sacchetti on 6/19/2007.

Dr. Sacchetti declares that the Bowen patent describes a method for generating dopaminergic cells by the introduction and endogenous expression of Nurr1 in CNS stem cells. Bowen also mentions that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media from striatal astrocytes or striatal membranes or extracts has been shown to increase the survival of the neurons (See column 3, lines 11-25). Dr. Sacchetti declares that this was not addressed experimentally in the context of Nurrl and was only mentioned as introduction. Dr. Sacchetti declares that the idea behind that suggestion is also different from the invention claimed in the '913 application. Bowen proposed striatal cells because they are known to be the source of target-derived neurotrophic factors that promote survival of neurons and their subsequent morphological differentiation. Thus both the striatal cells suggested by Bowen, and the purpose of that suggestion (neurotrophic support) are different from the cells used and required for use in the Arenas invention (Type 1 astrocytes of the ventral mesencephalon) and the purpose (instruct development of progenitor cells).

Dr. Sacchetti declares that Bowen achieved poor results. Nurr1 was simply transduced into cells and in a typical experiment only 3.5% TH^+ cells were obtained out of the total Nurr1 positive cells by 3 d after transfection" (example 3). Dr. Sacchetti declares that the protocol of Professor Arenas and colleagues allows one to obtain 90%

TH^+ cells out of the total cells in the culture, suggesting that this protocol has virtually complete control over the variables involved in the process (Nurr1 + all VM astrocyte secreted factors), whereas that by Bowen only takes in account one parameter (knurl).

Dr. Sacchetti declares that Takeshima has treated different cells from those used in the method claimed in the '913 application (neurons instead of progenitors), and for a different purpose. In the Arenas invention, Type 1 astrocytes of the ventral mesencephalon are employed to provide midbrain instructive factors to midbrain progenitors with the goal of inducing a dopaminergic fate and guiding progenitors in their development until they give rise to newborn dopamine neurons. Dr. Sacchetti declares that this is conceptually very different from providing survival-promoting factors to already born neurons.

Dr. Sacchetti notes that the entire protocol by Professor Arenas and colleagues focuses on a developmental time and a developmental process taking place *prior* to the events reported or suggested by either Bowen or Takeshima. Dr. Sacchetti submits that whereas Bowen and Takeshima were concerned with promoting survival of neurons, the protocol of Professor Arenas and colleagues is promoting the development of progenitors into dopaminergic neurons.

Dr. Sacchetti declares that Takeshima also did not use *Nurrl* in their protocol and did not examine for inductive signals. Takeshima treated cells that were already neuronal cells and then assayed for total numbers of TH^+ cells and not for the conversion of progenitors ($Nurr1^+$ / TH^- cells) into dopaminergic neurons ($Nurr1^+$ /TH^+ cells). The work of Takeshima gives no suggestion of the inductive activity found by

Professor Arenas and his colleagues. On the contrary, Takeshima emphasizes the neurotrophic effect of glia.

Dr. Sacchetti declares that the experiments described in the '913 application and in the inventors' paper Wagner *et al.* (1999) Nature Biotechnology 17, 635 - 636 were not obvious from data in the literature. Neurotrophic factors were expected to act on newborn neurons either in a target-derived fashion (hence the experiment suggested by Bowen) or possibly in a paracrine manner (hence the experiment performed by Takeshima). Both experiments focus on maintaining the survival of newborn dopaminergic neurons in a fashion similar to that proposed for glial cell-line derived neurotrophic factor (GDNF) in a paracrine manner on dopaminergic neurons and later on in the striatum, to work in a target-derived fashion. Professor Arenas and colleagues proposed that neurotrophic factors are not the critical factor and provided a different approach based on new insight: that progenitors do not develop properly per se *in vitro* and that an instructive factor needs to be supplied to cooperate with Nurr1. Dr. Sacchetti declares that this idea was new at that time and it is valid still today. Dr. Sacchetti declares that there is no suggestion in the disclosures of Bowen and Takeshima, considered individually or together, that a Type 1 astrocyte of the ventral mesencephalon could be used to provide an instructive factor to induce a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell.

Applicant's arguments filed 5/29/2007 have been fully considered but they are not persuasive. The Declaration under 37 CFR 1.132 filed 6/19/2007 is

insufficient to overcome the rejection of claims 1-3 and 5-12 based upon 35 U.S.C. 103(a) as set forth in the last Office action. The declaration will be discussed in detail below.

There appear to be multiple issues regarding the rejection by Bowen in view of Takeshima. One issue regards the identity of the cells that were co- cultured. The claims recite "a neural stem cell or neural progenitor cell". The instant specification defines neural stem cell as "any cell type that can divide more than once and can give rise to cells that exhibit the most primitive type of phenotypes for neurons, astrocytes and oligodendrocytes". The instant specification defines neural progenitor cell as a "multipotent daughter of a neural stem cell, which daughter is restricted in its potential fates and/or has a reduced proliferative potential compared to a neural stem cell". The E14 rat cells taught by Takeshima would meet the limitation of neural progenitor cell as defined in the instant specification.

Takeshima et al teach that the cells used in the experiments were obtained from the ventral mesencephalon of gestational day 14 rats because at this stage of embryonic development most of the TH^+ cells are found in this block of tissue (see page 812, left column 1st paragraph). Therefore, the cells used in the experiments taught by Takeshima are obtained from embryonic tissue. Takeshima et al does teach culturing of TH^+ cells, as well as examination and discussion of their developmental stages as suggested by the examiner. However, Takeshima et al teach that they observed an inconsistent increase in the percentage of TH+ neurons (see page 816, right column, 1st paragraph). An increase in the percentage of TH^+ neurons suggests that cells that were

not previously TH^+ cells differentiated from the starting embryonic population. Furthermore, it is not necessary for Takeshima et al to use neural progenitor cells in the methods, because Bowen et al use CNS stem cells (see column 10, lines 15-25 for example) and it is the combination of the two references that render obvious the claimed methods.

While Applicants submit that Bowen discloses that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media has been shown to increase the survival of the neurons in the background section, (See column 3, lines 11-25), it is this disclosure that illustrates that such co-culturing methods were known in the art and were contemplated by Bowen et al.

Another issue regards the submission that the Examiner has utilized impermissible hindsight. Teaching of neural stem and progenitor cells by Takeshima et al or Bowen et al is discussed above. Bowen et al do exemplify induction of TH^+ immunoreactivity in CNS stem cells that have been transfected with a Nurr1 expression vector (see column 11, Example 2, lines 29-40, in particular).

As discussed above and in the Advisory Action mailed 9/13/2006, Bowen et al discloses increased survival of dopaminergic neurons when in co-culture with astrocytes (see column 3, lines 11-25), which suggests that Bowen et al contemplates co-culture of astrocytes with neurons. Takeshima et al uses a culture of mesencephalic Type 1 astrocytes to support the growth of dopaminergic neurons derived from embryonic rat brains (i.e. neural progenitor cells). The motivation to combine is the expected benefit of being able to produce a viable culture of dopaminergic neurons, suggested by Bowen et

al and actually exemplified by Takeshima. Both the Bowen et al and Takeshima et al references are focused on similar goals, to develop and support the growth of neurons in culture from precursor cells. Contrary to Applicants' argument, the method taught by Takeshima et al alone does not have to produce an end result of the claimed method (i.e. induction of a dopaminergic cell fate) only that astrocytes could be co-cultured with neural progenitor or stem cells to contact the stem or progenitor cells with secreted factors.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant has mentioned the U.S. Supreme Court decision in *KSR International Co. v Teleflex Inc.,* S.Ct. 2007 WL1237837 (U.S.). Bowen et al teach a method of directing cell fate for CNS stem cells by the introduction of a gene encoding Nurr1 in order to direct neuronal precursors to a dopaminergic cell fate, which is verified by expression of TH (See abstract, and examples 1 and 2, in particular). It was known in the art, as disclosed by Bowen et al, to co-culture dopaminergic neurons with astrocytes. Takeshima et al teach methods of co-culture with astrocytes. The method of

claim 1 comprises the step of expressing Nurr1, and co-culturing the cells with ventral mesencephalic astrocytes to contact the cell with factors secreted from the astrocyte. The claimed method does not specify a required role of the secreted factors from the astrocyte. It appears that the expression of Nurr1 would be able to induce production of dopaminergic cells as exemplified by Bowen et al. Takeshima et al teach a beneficial developmental effect on developing neurons by co-culture with astrocytes.

Applicants have cited *In re Avery*, wherein the obviousness issue stemmed from whether the teaching of the reference patent had use in the process of the primary reference. Applicants have also cited *Ex parte Stauber*, wherein the obviousness issue stemmed from whether there was a logical reason for the skilled artisan to apply the teachings at hand. Unlike *Avery* and *Stauber*, coculture with astrocytes provides neuronal cells with secreted factors, a teaching that was known in the art as disclosed by Bowen et al.

Since Bowen et al disclose that survival of dopaminergic neurons is increased by co-culture with astrocytes and Takeshima et al teach a benefit of coculture with astrocytes on developing neurons, it would be obvious to combine the teachings to render obvious the claimed methods because all of the claimed elements were known in the prior art and the skilled artisan could have combined the elements as claimed by known method with no change in the respective function and the combination would have yielded the predictable result of induction of a dopaminergic neuronal fate in a NSC or NPC to one of ordinary skill in the art at the time the invention was made.

Response to Arguments in the Sacchetti Declaration

Although Bowen discloses that methods of co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media, or membranes or extracts has been shown to increase the survival of the neurons (See column 3, lines 11-25) and not the claimed Type I astrocytes of the ventral mesencephalon as claimed, it is not necessary for Bowen et al to teach VM astrocytes in co-culture because Takeshima et al teach the use of astrocytes obtained from the ventral mesencephalon in a co-culture. It is the combination of the methods of Takeshima et al and Bowen et al that render obvious the claimed method.

Dr Sacchetti submits that Bowen et al achieved only poor results. However, Bowen et al is not an anticipatory reference and the claimed method does not require any limitation regarding the quantity of cells that would be induced to a dopaminergic neuronal fate. It is predictable that the combination of the method of Bowen et al and Takeshima et al would produce at least one dopaminergic neuronal cell.

Dr. Sacchetti discusses the issue that Takeshima has used neurons instead of progenitors. This issue has been discussed in detail above and is also applicable here. Dr. Sacchetti declares that the concept and purpose of the Arenas invention is very different from providing survival promoting factors to already born neurons. As discussed previously, the claims do not recite limitations for the purpose of the astrocyte co-culture or factors that would be secreted by the astrocytes, or recite limitations regarding a role, instructional or otherwise, for the secreted astrocyte factors.

Contrary to Dr. Sacchetti's submission that Bowen and Takeshima were concerned with promoting survival of neurons, rather than development of dopaminergic neurons, Bowen et al are very much concerned with causing stem cell to adopt a dopaminergic cell fate (see Abstract and Examples 1 and 2). The title of the Bowen Patent is "Method for generating dopaminergic cells derived from neuronal precursors".

Although Sacchetti declares that Takeshima also did not use *Nurrl* in their protocol and did not examine for inductive signals, it is the combination of the teaching of Bowen and Takeshima that renders obvious the claimed method and not individual references. Bowen et al teach the use of Nurr1 and therefore it is not necessary for Takeshima et al to do so. The cells used by Takeshima et al have been discussed in detail above and is also applicable here. Unexpected increase in total numbers of TH^+ cells as taught by Takeshima et al suggest that progenitor cells have been induced into dopaminergic neurons. Although Dr Sacchetti submits that the work of Takeshima gives no suggestion of the inductive activity found by Professor Arenas and his colleagues, the claimed method does not require that the coculture of astrocytes alone cause induction of TH^+ neurons, but in combination with overexpression of Nurr1.

Dr. Sacchetti discusses neurotrophic factors versus instructive factors in the claimed method. Dr. Sacchetti declares that there is no suggestion in the disclosures of Bowen et al and Takeshima et al, considered individually or together, that a VM Type 1 astrocyte could be used to provide an instructive factor to induce a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell.

As previously discussed, Bowen et al and Takeshima et al do not have to specifically teach that astrocyte could be used to provide an instructive factor to induce a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell. As written, the claims do not limit or specify the role of the factors secreted by the astrocytes as instructive or neurotrophic. The claims do not distinguish the specific roles of Nurr1 or the astrocyte secreted factors. The instant disclosure does not specifically teach that the factors secreted by the astrocytes are "instructive" and not neurotrophic. Although Arenas and colleagues proposed that progenitors do not develop properly per se *in vitro* and that an instructive factor needs to be supplied to cooperate with Nurrl, those specific limitations are not reflected in the claimed method as written. Therefore Bowen et al (of record) in view of Takeshima et al (of record) render obvious claims 1-3 and 5-12.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell, PhD
Examiner
8/28/2007

CELINE QIAN, PH D.
PRIMARY EXAMINER